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Heat capacity of methacetin in a temperature range of 6 to 300 K

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Abstract Heat capacity of methacetin (*N*-(4-methoxyphenyl)-acetamide) has been measured in the temperature range 5.8–300 K. No anomalies in the $C_p(T)$ dependence were observed. Thermodynamic functions were calculated. At 298.15 K, the values of entropy and enthalpy are equal to 243.1 J K^{-1} mol^{-1} and 36360 J mol^{-1}, respectively. The heat capacity of methacetin in the temperature range 6–10 K is well fitted by Debye equation $C_p = AT^3$. The thermodynamic data obtained for methacetin are compared with those for the monoclinic and orthorhombic polymorphs of paracetamol.

Keywords Adiabatic calorimetry · Methacetin · Heat capacity · Molecular crystals · Thermodynamic functions

Introduction

The dynamic properties of the compounds containing the acetamide group are attracting much interest. The acetamide group belongs to important molecular fragments, which are present in many drugs and proteins. Its dynamic properties are very sensitive to the presence of other groups linked to it by covalent bonds, as well as to the non-covalent interactions (first of all—hydrogen bonds), which this group forms with the surrounding species (solvent molecules in solutions, neighboring molecules in the crystals or glasses, excipients in the drug-excipient formulations) [1–7]. Thermodynamic properties have been studied in details for the polymorphs of paracetamol [8], which contains the acetamide group linked to a phenyl-ring, with an –OH substitute in the para-position (Fig. 1a). This –OH group is involved in the formation of two types of hydrogen bonds with the neighboring molecules acting simultaneously as a proton donor in a –OH···O=C– bond and a proton acceptor in a –NH···OH bond [9, 10]. This ability of the –OH group in paracetamol to form hydrogen bonds is of primary importance for the structures of its polymorphs [9, 10], their stability at variable temperature/pressure conditions [11–14] and lattice dynamics [6, 15].

It is possible to prepare a compound, in which the –OH group is substituted for an $–OCH_3$ group, so that the formation of the hydrogen bonds with the –OH group is no longer possible (Fig. 1b). This relatively small change in the molecular structure results in a complete rearrangement of the crystal structure: only one polymorph has been reported for methacetin, in which the molecules are linked in the infinite chains via the "peptide hydrogen bonds" –NH···O=C–.[1] These chains form almost flat, slightly undulating layers, in which the neighboring chains are

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[1] For a comparison, in the crystal structures of the polymorphs of paracetamol there are two-dimensional layers kept together via NH···O and OH···O hydrogen bonds (pleated in the monoclinic polymorph and flat in the orthorhombic one) [9, 10].

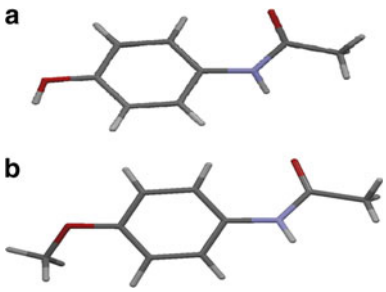

Fig. 1 Molecules of paracetamol (**a**) and methacetin (**b**)

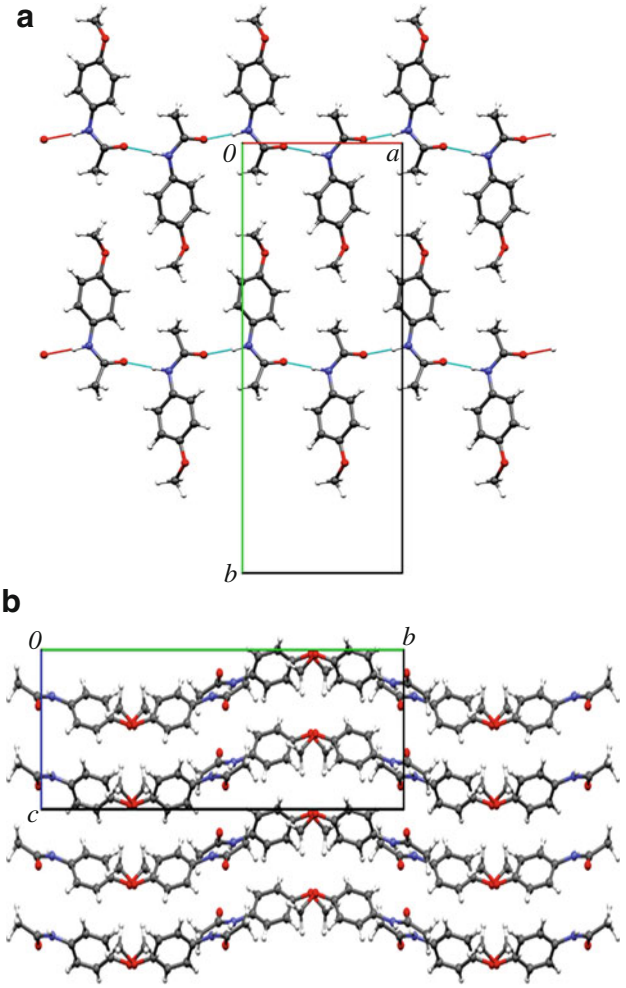

Fig. 2 The fragments of the crystal structure of methacetin in two projections

anti-parallel with respect to each other. There are only van der Waals interactions between the chains within a layer and between the layers (Fig. 2) [16].

Low-temperature calorimetry is well-established as a technique of choice to study the thermodynamic properties, dynamic, and polymorphic transitions, and subtle differences between related compounds (see [17–22] as examples).

The aim of this study was to study the heat capacity of this crystal in a wide temperature range by adiabatic calorimetry, to calculate the thermodynamic functions and to compare the results with those previously obtained for the two polymorphs of paracetamol [8].

Experimental

Sample

The sample of methacetin used in the study was synthesized from paracetamol, methyl-iodide, and potassium carbonate dissolved in acetone at 56 °C. The starting paracetamol reagent was purchased from Merck (99% pure). The product of the synthesis was re-crystallized from acetone (especially pure). The melting temperature of the final methacetin product after recrystallization was 129.0–130.0 °C. The powder X-ray diffraction analysis (Bruker GADDS, Cu K_α radiation) did not reveal the presence any other crystalline phases in the sample but the only known polymorph of methacetin.

Calorimetric measurement technique and results

The heat capacity was measured in the temperature range 5.8–300 K using a computerized vacuum adiabatic calorimeter [23]. The experiments were carried out in a pulse mode. The values of the heat capacity were measured at 71 points total. The results are summarized in Table 1. The standard deviation of the experimental points from the smoothed $C_p(T)$ curve was equal to 0.2% and 0.05% at 6–20 K and 20–300 K, respectively. The $C_p(T)$ was smooth in all the studied temperature range, no anomalies could be observed (Fig. 3). The smoothed values of the C_p and the calculated thermodynamic parameters at selected temperatures are summarized in Table 2. Thermodynamic parameters were calculated extrapolating the measured $C_p(T)$ curve from 5.8 K down to 0 K using the Debye function.

The $C_p(T)$ measured for methacetin was compared with the results, which were previously obtained for the monoclinic and the orthorhombic polymorphs of paracetamol [8]. A molecule of methacetin has three atoms more than that of paracetamol, and therefore, its molar heat capacity is higher, than that of paracetamol. If the values of heat capacity are normalized to the gram-atom of the compounds, the $C_p(T)$ curves of the polymorphs of paracetamol and methacetin become much closer, but are still not identical. Largest difference is observed at the very low temperatures (Fig. 4a). The difference between the

Table 1 Experimental heat capacity of methacetin

T/K	C_p/ J mol^{-1} K^{-1}	T/K	C_p/ J mol^{-1} K^{-1}	T/K	C_p/ J mol^{-1} K^{-1}
	Series 1	261.72	199.9	19.24	12.30
294.27	220.6	271.65	206.2	20.99	14.40
297.21	222.6	281.56	212.6	23.07	16.95
300.18	224.6	291.47	219.0	25.14	19.51
	Series 2		Series 3	27.46	22.40
84.86	82.03	164.83	138.5	30.03	25.63
89.99	86.19	167.85	140.4	32.60	28.89
95.13	90.28	170.85	142.4	35.17	32.08
101.20	94.86	173.82	144.5	37.72	35.24
108.21	100.1	176.76	146.9	41.04	39.16
115.19	105.1	179.74	148.0	45.12	43.92
122.16	110.0	182.76	149.9	49.17	48.42
129.16	114.8		Series 4	57.80	57.50
136.10	119.5	5.77	0.4959	62.84	62.44
143.01	124.1	6.87	0.8625	67.86	67.28
152.37	130.3	7.98	1.367	72.88	71.83
162.29	136.8	9.39	2.226	78.00	76.22
172.27	144.1	10.45	3.012	83.07	80.58
182.24	149.5		Series 5		Series 6
192.15	155.8	9.34	2.192	49.23	48.45
202.09	162.0	10.62	3.144	51.39	50.87
212.06	168.4	11.94	4.277	53.51	53.09
221.99	174.6	13.41	5.726	55.61	55.29
231.90	180.9	14.68	7.046		Series 7
241.85	187.3	16.10	8.627	296.23	221.92
251.80	193.6	17.67	10.43	299.19	223.79

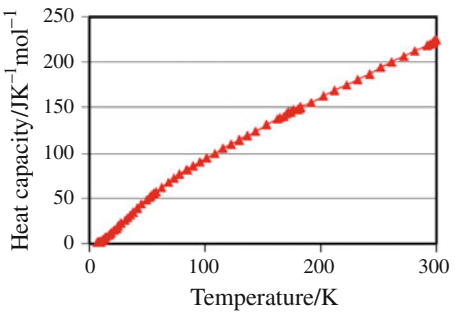

Fig. 3 Heat capacity of methacetin at temperatures from 6 to 300 K

normalized values of $C_p(T)$ measured for methacetin and for the polymorphs of paracetamol is well-visualized if plotted in per cent (Fig. 4b), similarly to the visualization of the difference in $C_p(T)$ for the two polymorphs of paracetamol done in [8]. It is interesting to note that the difference between the normalized $C_p(T)$ values has two extremes—a broad maximum at about 200 K, and a sharper minimum at 50 K. Besides, the difference changes its sign twice—first at about 100 K, and then at about 25 K. The largest difference is equal to −10% at about 50 K and reaches +20% at very low temperatures. Thus, although it is molecular structure that seems to have major effect on the $C_p(T)$ values, crystal packing and hydrogen bond pattern also are of importance in defining fine features of the crystal dynamics.

In Fig. 5 one can see the values C_p/T plotted versus T^2, in order to test the applicability of Debye cubic law to describing the behavior of low-temperature heat capacity of methacetin. The experimental data at temperatures 6–10 K can be fitted by a straight line going through the origin. The same is observed for paracetamol polymorphs. Thus, the $C_p(T)$ dependence for methacetin can be well described by Debye equation in the temperature range 6–10 K. The same holds for paracetamol polymorphs.

Table 2 Thermodynamic functions of methacetin

T/K	$C^0_{p,m}(T)$/ J K^{-1} mol^{-1}	$S^0_m(T) - S^0_m(0)$/ J K^{-1} mol^{-1}	$H^0_m(T) - H^0_m(0)$/ J mol^{-1}
5.77	0.4971	0.1657	0.7176
10	2.665	0.8862	6.673
15	7.396	2.802	31.10
20	13.20	5.711	82.35
25	19.34	9.312	163.6
30	25.61	13.39	275.9
35	31.86	17.81	419.6
40	37.93	22.46	594.2
45	43.76	27.27	798.5
50	49.33	32.17	1031
60	59.71	42.10	1577
70	69.21	52.02	2223
80	77.98	61.84	2959
90	86.21	71.51	3781
100	93.98	81.00	4682
120	108.5	99.43	6709
140	122.1	117.2	9016
160	135.4	134.4	11590
180	148.3	151.1	14430
200	160.8	167.3	17520
220	173.4	183.3	20860
240	186.1	198.9	24460
260	198.8	214.3	28310
280	211.6	229.5	32410
298.15	223.2	243.1	36360
300	224.4	244.5	36770
300.18	224.5	244.6	36810

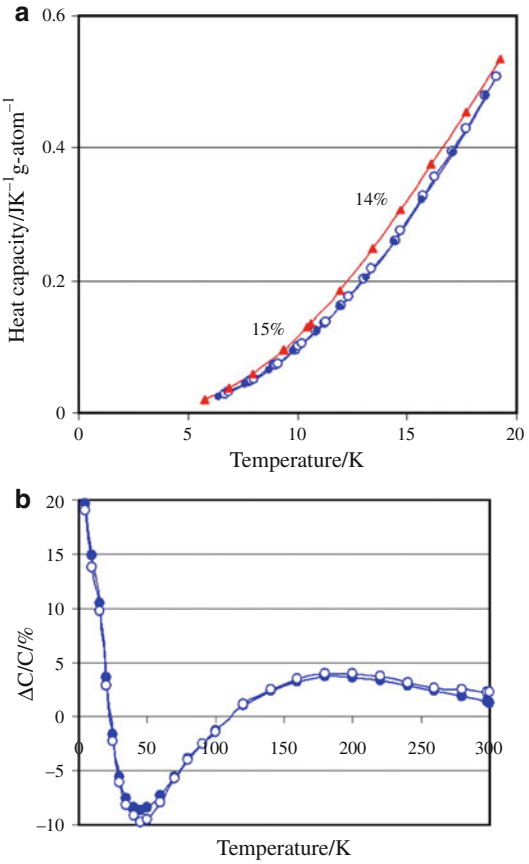

Fig. 4 **a** Comparison of normalized heat capacities of methacetin and paracetamols at low temperatures. **b** The difference between normalized C_p of methacetin and that of the polymorphs of paracetamol relative to C_p of methacetin. *Open circles* monoclinic and *filled circles* orthorhombic paracetamol

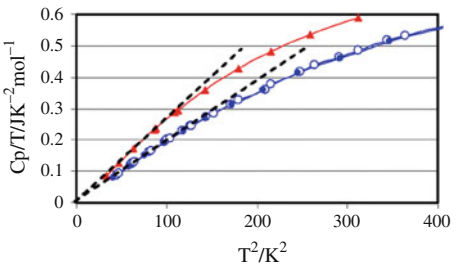

Fig. 5 A test for the applicability of Debye model to describing the low-temperature heat capacity: *triangles* methacetin, *open circles* monoclinic, and *filled circles* orthorhombic paracetamol

Conclusions

Thermodynamic properties of methacetin have been studied at 5.8–300 K. The $C_p(T)$ does not show any anomalies in this temperature range. Thermodynamic functions are calculated, including their values at 298.15 K. The $C_p(T)$ of methacetin has been compared with the dependences for the two polymorphs of paracetamol. The values of heat capacity for the three structures normalized to the gram-atom were quite close, but still not identical. A better visualization of the difference between the normalized $C_p(T)$ values for methacetin and for the polymorphs of paracetamol (plotted in per cent) is presented in Fig. 4b. This difference ΔC/C has revealed two extremes—a broad maximum at about 200 K, and a sharper minimum at 50 K. Besides, the difference changed its sign twice—first at about 100 K, and then at about 25 K. Thus, although it is molecular structure that seems to have major effect on the $C_p(T)$ values, crystal packing and hydrogen bond pattern also are of importance in defining fine features of the crystal dynamics. The $C_p(T)$ dependence for methacetin can be well described by Debye equation in the temperature range 6–10 K.

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